The American Journal of Cardiology 254 (2025) 32–41

Contents lists available at ScienceDirect

The American Journal of Cardiology

journal homepage: www.elsevier.com/locate/ajc

Expert review

Direct Oral Anticoagulants Versus Low-Molecular-Weight Heparin in Patients With Cancer-Associated Thrombosis: A Meta-Analysis of Randomized Controlled Trials

Asma Mousavi, MD[a,b], Shayan Shojaei, MD[a,b*], Soheil Rahmati, MD[a], Parham Dastjerdi, MD[a,c], Mahshad Sabri, MD[d], Keyvan Salehi, MD[a,e], Kasra Izadpanahi, MD[a,b], Homayoun Pishraft-sabet, MD[a,b], Elmira Jafari Afshar, MD[f], Mahsa Noohi Arbatan, MD[b], Marc Samsky, MD[g], Kolte Dhaval, MD[h], Jamal Rana, MD[i], Toshiki Kuno, MD[h], Jay Giri, MD[j], Kaveh Hosseini, MD[a]

[a] *Tehran Heart Center, Cardiovascular Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran*
[b] *School of Medicine, Tehran University of Medical Sciences, Tehran, Iran*
[c] *Department of Cardiovascular Diseases, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran*
[d] *Rajaei Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran*
[e] *School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[f] *Cardiovascular Research Center, Alborz University of Medical Sciences, Alborz, Iran*
[g] *Yale University School of Medicine, New Haven, Connecticut, US*
[h] *Cardiology Division, Massachusetts General Hospital and Harvard Medical School, Boston, US*
[i] *Kaiser Permanente Oakland Medical Centre, Oakland, US*
[j] *Director of Cardiovascular Catheterization Laboratories, Hospital of the University of Pennsylvania, Philadelphia, US*

ARTICLE INFO

Article History:
Received 6 March 2025
Revised 10 June 2025
Accepted 21 June 2025

Keywords:
cancer-associated thrombosis
direct oral anticoagulants
low-molecular-weight heparin
meta-analysis

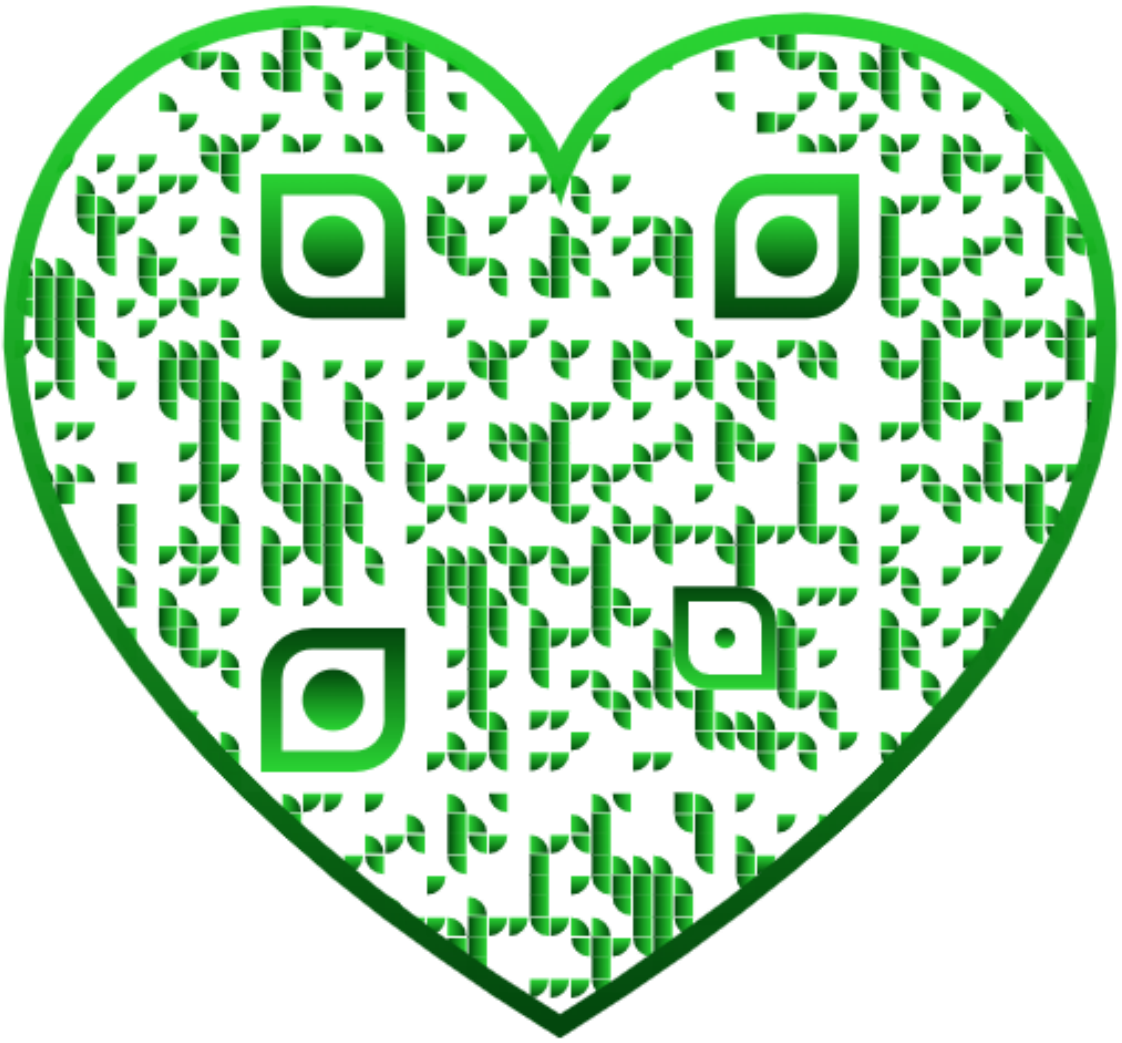
Cancer-associated thrombosis (CAT) is a significant cause of morbidity and mortality in patients with cancer. Determining the optimal anticoagulant remains a clinical challenge. This meta-analysis aimed to compare the efficacy and safety of direct oral anticoagulants (DOACs) and low-molecular-weight heparin (LMWH) for CAT treatment. We systematically searched databases for randomized controlled trials (RCTs) comparing DOACs and LMWH in patients diagnosed with CAT. Efficacy outcomes were recurrent venous thromboembolism (VTE), deep vein thrombosis (DVT), and pulmonary embolism (PE). Safety outcomes comprised total bleeding, major bleeding, clinically relevant nonmajor bleeding (CRNMB), and all-cause mortality. We calculated incidence risk ratios (IRRs) with 95% confidence intervals (CIs) using a random-effects model. Subgroup analyses were conducted based on administered DOAC type. We identified 10 RCTs with 4713 participants (mean age 64.63 years, 50.58% male), including 2390 receiving DOACs and 2323 receiving LMWH. Compared to LMWH, the DOACs group demonstrated a statistically significant reduction in the incidence of VTE (IRR = 0.66, 95% CI 0.56 to 0.79). Total bleeding (IRR = 1.10, 95% CI 0.80;1.50) and mortality (IRR = 1.00, 95% CI, 0.89–1.12) did not differ significantly. Sensitivity analyses of studies with >100 participants and 6-month follow-up were consistent with overall results. In conclusion, DOACs were more effective than LMWH in reducing the risk of recurrent VTE and DVT in patients with CAT, with comparable safety profiles. The improved efficacy of DOACs positions them as a potentially advantageous therapeutic option for this patient population. Further research is warranted to optimize DOAC use in different cancer types and patient subgroups.

© 2025 Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

Malignancy significantly increases the risk of venous thromboembolism (VTE), a major cause of morbidity and mortality in cancer patients and the second leading cause of death in this population.[1] The pathogenesis of cancer-associated thrombosis (CAT) is multifactorial, involving patient vulnerabilities, tumor characteristics, and cancer therapies, all contributing to increased thrombotic risk.[2,3] Patients with a history of CAT have a disproportionately higher incidence of recurrent VTE and major bleeding events,[4] which are associated to reduced survival, increased hospitalizations, and disruptions in anticancer treatments.[2] Given the necessity for extended anticoagulation in CAT management, identifying optimal and safe therapeutic strategies is paramount.[5] Historically, vitamin K antagonists

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
*Corresponding author.
E-mail address: s.shojaei.id@gmail.com (S. Shojaei).

https://doi.org/10.1016/j.amjcard.2025.06.022
0002-9149/© 2025 Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies.



(VKAs) like Warfarin and subcutaneous low-molecular-weight heparin (LMWH) were the primary outpatient treatments for VTE in CAT.[5] However, direct oral anticoagulants (DOACs) have emerged as a promising alternative, indicating efficacy and safety profiles that warrant their consideration as first-line therapy in many clinical situations.[6–9] DOACs offer the convenience of oral administration, eliminating injections, and potentially improving adherence.[10] Nevertheless, guidelines highlight important differences between DOACs and LMWH, recommending LMWH for patients with severe renal impairment or high gastrointestinal bleeding risk, where DOACs may be contraindicated.[11,12] Given these persistent uncertainties and the complexity of managing CAT, current guidelines often recommend indefinite anticoagulation for patients with active malignancy, thrombophilia, unprovoked thromboses, metastatic disease, or those actively undergoing chemotherapy. Therefore, to address this knowledge gap and provide evidence-based guidance, we conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) comparing the efficacy and safety of DOACs versus LMWH in the treatment of patients diagnosed with CAT.

Methods

Literature search strategy

A comprehensive systematic literature search was executed to identify relevant studies. This search encompassed the following databases: PubMed, Scopus, Web of Science, and Embase until December 2024. To ensure exhaustive coverage, the reference list of all included studies and related review articles were also examined for additional RCTs. The full search strategy is provided in Supplementary Table 1.

Protocol

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria.[13] The protocol for this systematic review and meta-analysis is submitted to the prospective register of systematic reviews (PROSPERO ID: CRD42025630507).[14]

Study selection criteria

Four independent reviewers (H.P., S.R., K.I., and P.D.) initially screened articles based on titles and abstracts, followed by a full-text assessment. Discrepancies were resolved through consensus with 2 reviewers (S.S. and A.M.). The Rayyan online platform was used for the screening process.[15] The following inclusion and exclusion criteria were applied:

- Inclusion criteria: RCTs directly comparing the efficacy and safety of DOACs (Dabigatran, Rivaroxaban, Apixaban, Betrixaban, and Edoxaban) with LMWH (Enoxaparin, Dalteparin, Tinzaparin, and Nadroparin) in patients diagnosed with CAT.
- Exclusion criteria: Case reports, reviews, non-RCT original studies, letters to the editor, conference abstracts, book chapters, noncomparative studies, animal studies, and studies investigating anticoagulants for prophylactic rather than therapeutic purposes.

Outcome measures

The efficacy outcome was defined as the incidence of thromboembolic events following the initiation of anticoagulation therapy. These events included: recurrent VTE, recurrent deep vein thrombosis (DVT), and recurrent pulmonary embolism (PE). The safety outcomes included total bleeding events (encompassing major bleeding and clinically relevant nonmajor bleeding (CRNMB)), and mortality. Bleeding events were defined according to the criteria established by the International Society on Thrombosis and Haemostasis (ISTH).[16,17]

Data extraction

Two reviewers (S.S. and S.R.) independently assessed the included articles and extracted data. Extracted data included: the first author's name and publication year; the study's inclusion and exclusion criteria; the distribution of gender within each arm; the duration of follow-up; the mean body mass index (BMI) for each intervention group; relevant patients' medical history (e.g. presence of diabetes mellitus (DM), hypertension (HTN)); the duration of anticoagulation therapy; specific anticoagulant medication and dosages; indications for anticoagulation; details regarding cancer type and stage, and presence of metastases; and finally, the reported efficacy and safety outcomes. The extracted data were rechecked by a third reviewer (A. M.). In this study, the case group received DOAC therapy, while the control group underwent LMWH therapy.

Risk of bias assessment

The methodological quality of included RCTs was rigorously assessed using the Cochrane Risk of Bias 2 (RoB2) tool.[18] This tool evaluated 5 domains to assess the risk of bias arising from: the randomization process; deviations from the intended interventions; missing outcome data; measurement of outcomes; and the selection of reported results. Two reviewers completed the assessment (K.I. and A.M.) independently and checked the discrepancies by a senior reviewer (K.H.).

Statistical analysis

All meta-analyses were performed using the R software (version 4.3.3) with the `meta` package.[19] We calculated incidence rate ratios (IRRs) with 95% confidence intervals (CIs) for dichotomous outcomes, using person-time (in person-months, calculated as the number of participants multiplied by follow-up duration in months) to account for varying follow-up periods across studies. IRRs were pooled using a random effects model with inverse variance weighting.[20] The Hartung-Knapp-Sidik-Jonkman (HK) method was applied to adjust CIs, providing more conservative estimates, particularly for analyses with small numbers of studies.[21] The I^2 statistic and associated p-value were calculated to assess the degree of heterogeneity present, with I^2 values above 50% considered to signal significant heterogeneity.[22] We conducted subgroup analyses by intervention type (apixaban, rivaroxaban, and other DOACs) to explore potential differences in treatment effects. Leave-one-out (LOO) sensitivity analyses were conducted for all outcomes to assess the influence of individual studies on pooled estimates. We also performed a sensitivity analysis restricted to RCTs with a 6-month follow-up, calculating IRRs with person-time fixed at 6 months per participant. To evaluate the impact of small studies, we conducted an additional sensitivity analysis excluding RCTs with a total sample size of less than 100. Publication bias was evaluated for primary outcomes (total bleeding and VTE) using contour-enhanced funnel plots and Egger's regression test.[23] All statistical tests were 2-sided, with $p < 0.05$ considered statistically significant.

Results

Our comprehensive search across databases yielded 1,930 studies. After removing duplicates and screening titles/abstracts, we selected

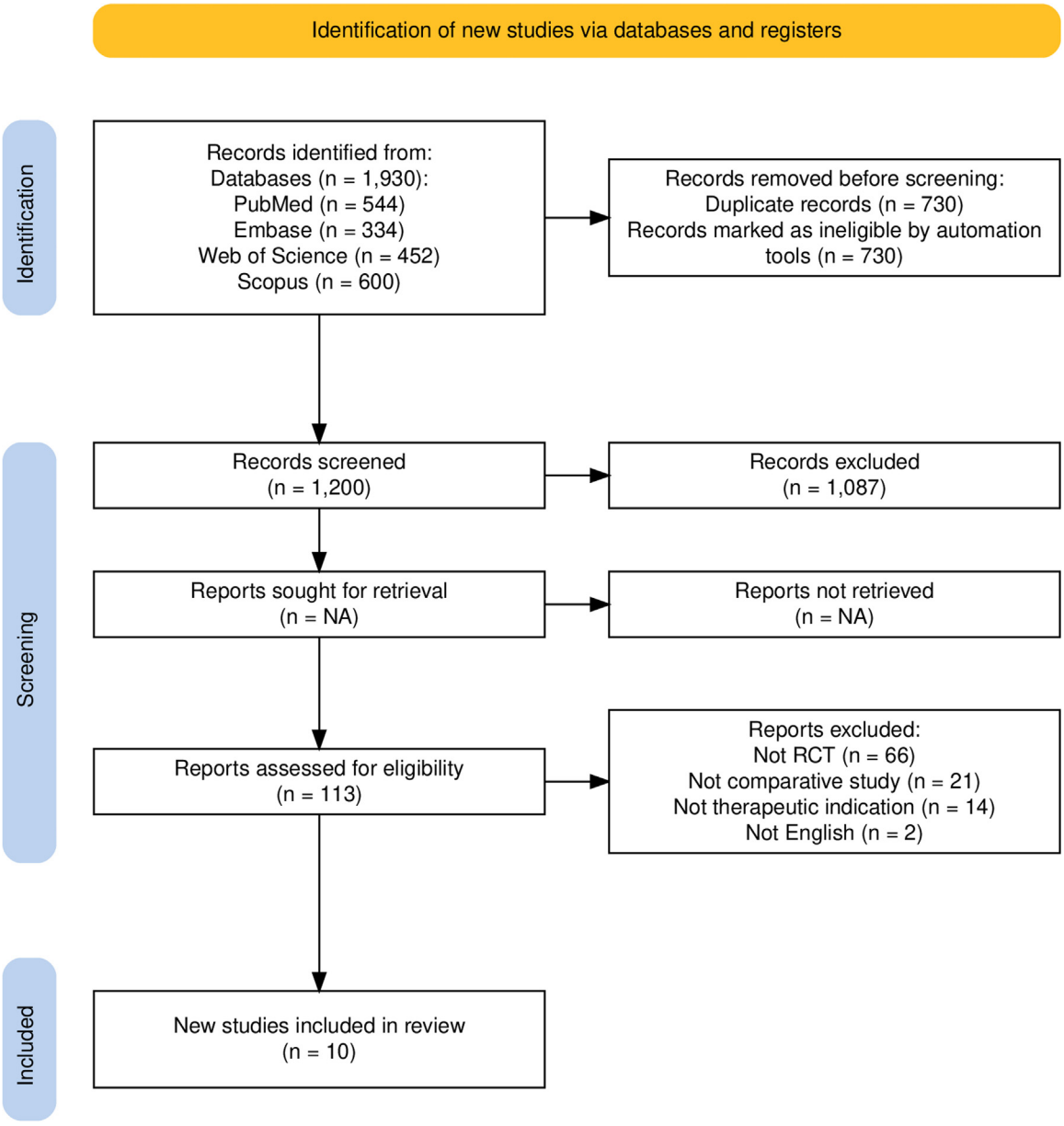


Figure 1. PRISMA flow chart. RCT = randomized controlled trial.

113 studies for full-text screening. A detailed review of remained studies resulted in the inclusion of 10 RCTs in our meta-analysis based on our inclusion criteria. The PRISMA flowchart depicts the study selection process (Figure 1).

Baseline characteristics

The 10 RCTs included in our meta-analysis involved 4713 participants, with a mean age of 64.63 years and 50.58% male. Among these individuals, 2390 were in the DOAC group, and 2323 were in the LMWH group. The studies were conducted in various locations: 4 were multinational,[6,9,24,25] 2 were from the USA,[7,26] and the remaining ones were from Korea,[11] France,[27] Egypt,[28] and the UK.[8] The initiation of anticoagulants was related to CAT incidence. The follow-up duration across the included studies ranged from 3 months to 12 months. Details about the cancer types, anticoagulant types and dosages, and history of VTE in the included studies are summarized in Table 1.

Risk of bias assessment

The quality assessment of the included studies revealed that 6 out of 10 studies[6,9,24–27] had a low risk of bias, 1 study[8] had some concern, and 3 studies[7,11,28] had a high risk of bias. The primary concerns were related to domains 2 (deviation from intended intervention) and 3 (missing outcome data). Supplementary Figure 1 provides a detailed summary of the risk of bias assessment for the studies.

Efficacy and safety outcomes

The comparison of DOAC with LMWH in patients with CAT reveals that DOACs are associated with a significantly lower incidence of VTE (IRR = 0.66, 95% CI, 0.56;0.79) based on 10 RCTs (Figure 2a). Specifically, while the incidence of PE and DVT showed nonsignificant differences separately (IRR = 0.71, 95% CI 0.47;1.08 and IRR = 0.58, 95% CI 0.32;1.04), respectively (Figures 2b and c). Regarding safety, both groups exhibited similar total bleeding rates (IRR = 1.10, 95% CI 0.80

Table 1
Baseline characteristics of included studies

Study characteristics				Case group						Control group					
Author	Country	Cancer type	Follow-up (months)	N	Anticoagulant name and dosage	Mean age	Male (%)	History of previous PE (%)	History of previous DVT (%)	N	Anticoagulant name and dosage	Mean age	Male (%)	History of previous PE (%)	History of previous DVT (%)
Schrag[26]	USA	Solid tumors, lymphoma, chronic lymphocytic leukemia, and multiple myeloma	6	330	Various DOACs	64	149 (45%)	190 (58%)	134 (41%)	308	Various LMWHs	62	136 (44%)	174 (56%)	127 (41%)
Planquette[27] (CASTADIVA trial)	France	Solid and hematologic malignancies	3	74	Rivaroxaban 15mg BD for the first 3 weeks and then 20 mg daily	69	37 (50%)	67 (91%)	32 (43%)	84	Dalteparin 200 IU /kg for 1 month and then 150 IU/kg	71	40 (48%)	69 (82%)	37 (44%)
Kim[11] (Priority trial)	Korea	Upper GI tract, hepatobiliary, and pancreatic cancer	6	44	Rivaroxaban 15 mg BD for 3 weeks and then 20 mg daily, or Apixaban 10 mg BD for the first 7 days and then 5 mg BD	61	25 (57%)	35 (80%)	4 (9%)	46	Daleteparin 200 IU/kg daily for 1 month and then 150 IU/kg daily	62	23 (50%)	32 (70%)	10 (21%)
Mokadem[28]	Egypt	Solid malignancies	6	50	Apixaban 10 mg BD for 7 days and then 5 mg BD	61	20 (40%)	NA	NA	50	Enoxaparin subcutaneously 1mg/kg BD	60	22 (44%)	NA	NA
Agnelli[6] (Caravaggio trial)	Multinational	Solid and hematologic malignancies	6	576	Apixaban 10mg BD for 7 days and then 5mg BD	67	292 (51%)	30 (53%)	272 (47%)	579	Dalteparin 200 IU/kg subcutaneously daily for 1 month and then 150 IU/kg daily	67	276 (48%)	334 (58%)	245 (42%)
Mcbane II[7] (ADAMVTE trial)	USA	Solid and hematologic malignancies	6	145	Apixaban 10 mg BD for 7 days and then 5 mg BD	64	72 (48%)	81 (55%)	71 (48%)	142	Dalteparin 200 IU/KG daily for 1 month and then 150 IU/kg daily	64	73 (49%)	75 (51%)	70 (47%)
Raskob[9] (Hokusai trial)	Multinational	advanced cancers	12	522	Edoxaban 60 or 30 mg daily	64	277 (53%)	328 (63%)	194 (37%)	524	Dalteparin 200 IU /kg for 1 month and then 150 IU/kg	64	263 (50%)	329 (63%)	195 (37%)
Young[8] (SELECT-D trial)	United Kingdom	Solid and hematologic malignancies	6	203	Rivaroxaban 15mg BD for 3 weeks and then 20 mg daily	61	116 (57%)	145 (71%)	53 (25%)	203	Dalteparin 200 IU/kg subcutaneously daily for 30 days and then 150 IU/kg subcutaneously daily	64	98 (48%)	150 (73%)	57 (28%)
Agnelli[6] (AMPLIFY trial)	Multinational	Prostate, breast, colon, bladder, and lung cancer	6	88	Apixaban 10mg BD for 7 days and then 5mg BD	66	50 (57%)	64 (73%)	62 (70%)	81	Enoxaparin 1 mg/kg BD for at least 5 days	65	49 (61%)	51 (63%)	54 (67%)
Prins[25]	Multinational	Active cancer	12	353	Rivaroxaban 15 mg BD for 21 days and then 20 mg daily	NA	209 (59%)	NA	NA	298	Enoxaparin subcutaneously 1 mg/kg BD for at least 5 days	NA	160 (53%)	NA	NA

Abbreviations: BD = twice daily; DOAC = direct oral anticoagulant; DVT = deep vein thrombosis; GI = gastrointestinal; LMWH = low-molecular-weight heparin; PE = pulmonary embolism.

−1.50), and major bleeding rates were comparable (IRR = 1.00, 95% CI 0.59−1.69) (Figures 3a and b). However, CRNMB was more frequent with DOACs (IRR = 1.68, 95% CI 1.20−2.35), indicating superior safety of LMWH in this aspect (Figure 3c). Mortality rates did not differ significantly between the groups (IRR = 1.00, 95% CI 0.89−1.12) (Figure 4). Table 2 summarizes the efficacy and safety outcomes.

Subgroup analysis

Subgroup analyses were conducted to evaluate the efficacy and safety of DOACs compared to LMWH based on the type of DOAC administered. These analyses aimed to determine if the outcomes observed in the overall analysis varied across different subgroups. Based on different types of DOACs administered, including Apixaban, Rivaroxaban, and others, the results showed that the superior efficacy of DOACs over LMWH in reducing VTE incidence was significant in the subgroup of other DOACs, but nonsignificant in the Apixaban and Rivaroxaban subgroups (Supplementary Figure 2). In the subgroup analyses for DVT and PE outcomes, the results were consistent with those of the overall analysis (Supplementary Figures 3 and 4). Furthermore, subgroup analyses based on the type of DOAC were conducted to assess safety outcomes. The results showed that total bleeding and major bleeding rates were consistent with the overall analysis (Supplementary Figures 5 and 6). However, the incidence of CRNMB was nonsignificant across all subgroups, despite showing a significant difference in the overall analysis (Supplementary Figure 7) (Table 3).

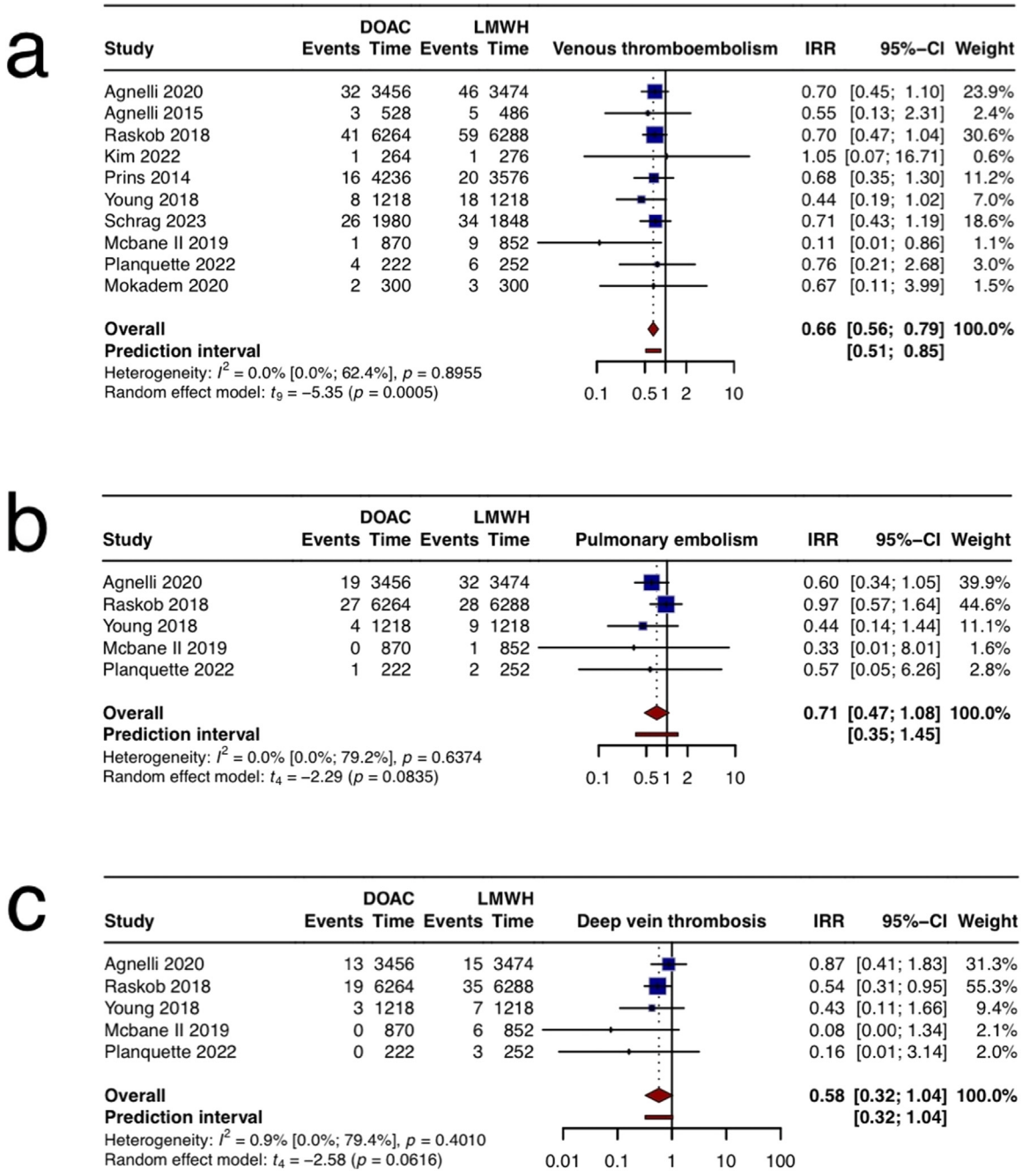
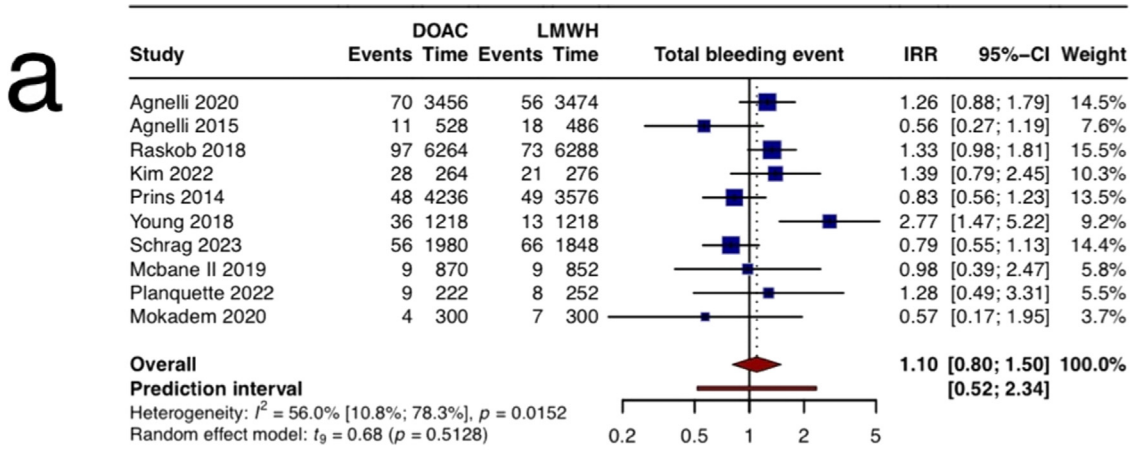
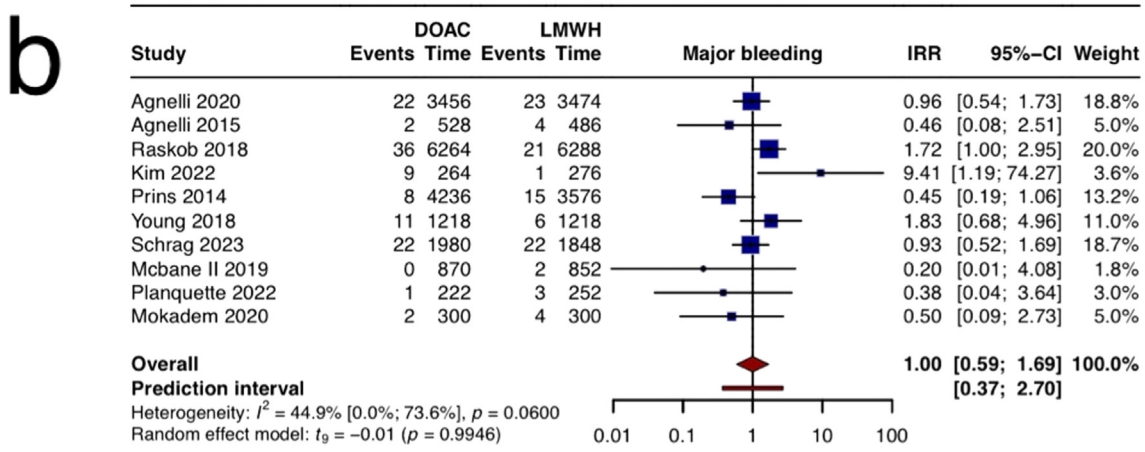


Figure 2. Efficacy outcomes comparison between DOACs and LMWH. a) Venous thromboembolism forest plot b) Pulmonary embolism forest plot c) Deep vein thrombosis forest plot. CI = confidence interval; DOAC = direct oral anticoagulants; IRR = incidence rate ratio; LMWH = low-molecular weight heparin.





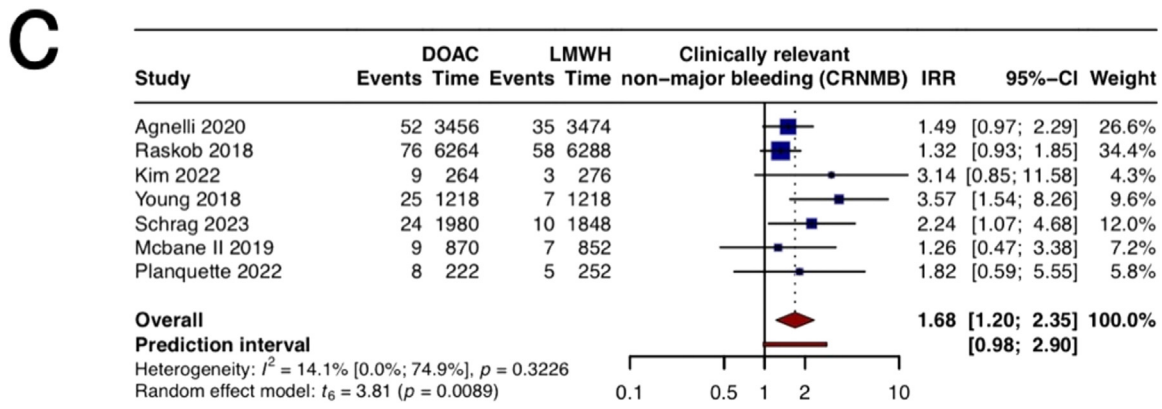


Figure 3. Bleeding events comparison between DOACs and LMWH. a) Total bleeding forest plot b) Major bleeding forest plot c) Clinically relevant nonmajor bleeding forest plot. CI = confidence interval; DOAC = direct oral anticoagulants; IRR = incidence rate ratio; LMWH = low-molecular weight heparin.

Sensitivity analysis

Sensitivity analyses excluding studies with fewer than 100 participants yielded results consistent with the overall analysis across all outcomes (Supplementary Figures 8-14). Furthermore, sensitivity analyses by limiting including studies into studies with follow-up of 6 months, showed similar results as overall analysis in all outcomes, except PE analysis which demonstrated significantly higher risk of PE in LMWH group compared to DOAC group (IRR = 0.56, 95% CI, 0.36–0.86) (Supplementary Figures 15–21). Additionally, sensitivity analyses using the LOO method showed that by omitting 1 of the included studies[9] from the PE incidence analysis, the result altered to be statistically significant in favor of DOACs (IRR = 0.56, 95% CI, 0.43–0.72) (Supplementary Figure 6). However, the LOO analyses of other outcomes remained consistent with the overall analysis (Supplementary Figures 22–28).

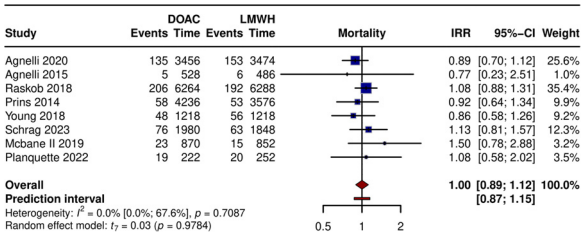


Figure 4. Mortality outcome comparison between DOACs and LMWH. CI = confidence interval; DOAC = direct oral anticoagulants; IRR = incidence rate ratio; LMWH = low-molecular weight heparin.

Publication bias

Funnel plots and Egger tests indicated low publication bias for VTE and total bleeding outcomes (Supplementary Figures 29 and 30).

Discussion

Our meta-analysis comparing DOACs and LMWH in patients with CAT highlights key differences in efficacy and safety. DOACs were associated with a significantly lower overall incidence of recurrent VTE compared to LMWH, while PE and DVT incidence remained similar between the both groups. Regarding safety, both therapies showed comparable rates of major bleeding and total bleeding events. However, CRNMB was more frequent with DOACs, suggesting that LMWH may have a more favorable safety profile in this aspect. Mortality rates were similar between the both treatment groups, and subgroup analyses confirmed that these safety findings remained consistent across DOAC types. To our knowledge, this is the most comprehensive systematic review and meta-analysis to date comparing the efficacy and safety of DOACs and LMWH in patients with CAT. Our findings support the increased utilization of DOACs for recurrent VTE prevention and treatment in patients with cancer, particularly for their efficacy in reducing recurrent DVT.

Regarding efficacy outcomes, the findings of our study can be contextualized within prior systematic reviews and meta-analyses. Baloch et al. reported a statistically significant reduction in recurrent VTE with Apixaban compared to LMWH, as well as a borderline significant reduction in PE recurrence.[29] However, their results for DVT recurrence did not reach statistical significance. It is important to note that Baloch et al. included only 4 RCTs with a maximum of 1,632 patients in their analyses. In contrast, our meta-analysis incorporated 10 studies and 4,690 patients, offering stronger statistical power and a broader scope. Additionally, we provided detailed subgroup analyses based on DOAC type, which were not addressed in this review. Moreover, Elbadawi et al.[30] and Haykal et al.[31] both demonstrated that DOACs were associated with a lower incidence of recurrent VTE and DVT compared to LMWH while finding no significant difference in PE recurrence. Their findings align with our results, reinforcing the superior efficacy of DOACs in reducing VTE incidence without significantly impacting DVT and PE outcomes. Additionally, Elbadawi et al.[32] found no variation in efficacy among different types of DOACs, which is consistent with our findings. However, both analyses were based on the same 4 RCTs, with a total of 2,907 patients, whereas our meta-analysis incorporated a larger dataset. Furthermore, neither study examined the impact of follow-up durations on efficacy outcomes, a key aspect that we addressed by calculating IRR to provide a more comprehensive evaluation of treatment effects over time. A larger systematic review that included 6 RCTs reported findings consistent with ours. Their updated meta-analysis

Table 3
Subgroup analyses of outcomes based on DOAC type administration and follow-up duration

Outcome	Number of studies included	IRR	I2	*P*-value heterogeneity
		VTE		
Apixaban	4	0.64 (0.33–1.24)	1%	0.39
Rivaroxaban	3	0.60 (0.31–1.14)	0%	0.69
Other DOACs	3	0.71 (0.62–0.81)	0%	0.96
		PE		
Apixaban	2	0.59 (0.16–2.19)	0%	0.72
Rivaroxaban	2	0.47 (0.14–1.59)	0%	0.86
Other DOACs	1	0.97 (0.57–1.64)	-	-
		DVT		
Apixaban	2	0.39 (0.00–890553)	62%	0.11
Rivaroxaban	2	0.36 (0.00–38.46)	0%	0.56
Other DOACs	1	0.54 (0.31–0.95)	-	-
		Total bleeding		
Apixaban	4	0.90 (0.47–1.75)	35%	0.20
Rivaroxaban	3	1.40 (0.29–6.81)	80%	0.01
Other DOACs	3	1.12 (0.51–2.45)	64%	0.06
		Major bleeding		
Apixaban	4	0.81 (0.41–1.58)	0%	0.59
Rivaroxaban	3	0.77 (0.09–6.71)	58%	0.09
Other DOACs	3	1.62 (0.19–14.17)	65%	0.06
		CRNMB		
Apixaban	2	1.45 (0.66–3.21)	0%	0.76
Rivaroxaban	2	2.80 (0.05–173.09)	0%	0.34
Other DOACs	3	1.71 (0.63–4.60)	32%	0.23

Abbreviations: CI = confidence interval; CRNMB = clinically relevant nonmajor bleeding, DOAC = direct oral anticoagulant; DVT = deep vein thrombosis, IRR = incidence risk ratio; PE = pulmonary embolism, VTE = venous thromboembolism.

Table 2
Efficacy and safety outcomes

Outcome	Number of studies included	IRR (95% CI)	I2	*P*-value heterogeneity	*P*-value outcome
		Efficacy outcomes			
Total VTE	10	0.66 (0.56–0.79)	0%	0.90	<0.01
PE	5	0.71 (0.47–1.08)	0%	0.64	0.08
DVT	5	0.58 (0.32–1.04)	1%	0.40	0.06
		Safety outcomes			
Total bleeding	10	1.10 (0.80–1.50)	56%	0.02	0.51
Major bleeding	10	1.00 (0.59–1.69)	45%	0.06	0.99
CRNMB	7	1.68 (1.20–2.35)	14%	0.32	<0.01
All-cause mortality	8	1.00 (0.89–1.12)	0%	0.71	0.98

Abbreviations: CI = confidence interval; CRNMB = clinically relevant nonmajor bleeding; DVT = deep vein thrombosis; PE = pulmonary embolism; RR = risk ratio; VTE = venous thromboembolism.

demonstrated a significantly reduced risk of VTE, with no significant differences in major bleeding or mortality. In contrast, our analysis incorporated a greater number of RCTs, enabling more detailed subgroup analyses.

In terms of safety outcomes, our findings were generally consistent with prior systematic reviews and meta-analyses, though some differences emerged due to variations in study design and methodology. Moik et al.[33] reported that the risk of major bleeding was slightly higher in patients treated with DOACs compared to LMWH, although the difference was not statistically significant. Their analysis also found a significantly higher risk of CRNMB in patients treated with DOACs, which is consistent with our findings. However, their study only included 4 RCTs with a total of 2,894 patients, limiting the generalizability and statistical power of their results. By including up to 4,690 patients, our analysis offers a more comprehensive evaluation of safety outcomes and confirms the increased risk of CRNMB with DOACs while maintaining robust conclusions due to the larger dataset. Patel et al.[34] observed a nonsignificant increase in the risk of major bleeding with DOACs compared to LMWH, similar to our findings. Their subgroup analyses revealed contrasting results when comparing specific LMWH types: Enoxaparin was associated with a nonsignificant decrease in major bleeding risk with DOACs, while Dalteparin was linked to a significant increase. Our study, which exclusively included RCTs, did not conduct similar subgroup analyses due to the limited number of studies involving specific LMWH types. However, by restricting our inclusion criteria to RCTs, our findings provide higher reliability and lower bias compared to the Patel et al.[34] study, which also included observational studies. Song et al.[35] similarly concluded that DOACs did not significantly increase the risk of major bleeding compared to LMWH but highlighted an increased risk of CRNMB. Their subgroup analyses suggested that Rivaroxaban was associated with a higher risk of major bleeding and CRNMB compared to LMWH. While Song et al.[35] included both retrospective studies and RCTs, our analysis focused solely on RCTs to ensure methodological rigor. Unlike their study, we did not find significant variations in safety outcomes between different DOAC types. This discrepancy is likely due to the broader inclusion criteria in the Song et al.[35] study, which incorporated both retrospective and randomized studies, allowing for a larger dataset and potentially better-powered subgroup analyses of individual DOACs. Nevertheless, their findings may help guide future RCTs to evaluate specific DOAC subgroups in more detail.

The key differences between our study and prior systematic reviews and meta-analyses lie in the broader scope, larger number of included studies and patients, and more stringent inclusion criteria.[36,37] By focusing exclusively on RCTs and conducting detailed subgroup analyses, our meta-analysis provides a more comprehensive assessment of both efficacy and safety outcomes. Additionally, our study accounts for follow-up durations through sensitivity analyses and calculates IRR across different DOAC types, thereby enhancing the clinical applicability of our findings. By incorporating more recent and comprehensive data, our analysis offers a robust evaluation of DOACs versus LMWH in CAT.

The findings of our study showed that DOAC were better anticoagulants compared to LMWH at preventing recurrent VTE incidences, but differences in target study populations should also be taken into account. DOACs are contraindicated in several conditions such as renal and hepatic impairment, mechanical prosthetic valves, and moderate to severe mitral stenosis.[38] We focused on the ability of DOAC to prevent recurrent thromboembolic events in patients with CAT, however, we did not investigate this effect in other conditions requiring anticoagulation therapy such as acute myocardial infarction (MI) and bioprosthetic valves. One meta-analysis reported that a dual therapy of antiplatelet agents and DOACs after an episode of ST-elevation MI reduces subsequent ischemic events despite increasing the risk of major bleedings,[39] another recent study concluded the DOACs are noninferior to VKAs in patients with concomitant atrial fibrillation (AF) and bio-prosthetic valves in terms of reducing systemic embolic events[40]; however more well-designed studies are needed to conclude these drugs could be widely prescribed in such occasions. We did not have sufficient data to perform subgroup analysis for serious adverse outcomes such as fatal PE, VTE-related mortality, and bleeding-related mortality. Amin et al. reported there were no significant differences between DOAC and LMWH groups in terms of bleeding-related mortality[41]; Agnelli et al.[6] and Giustozzi et al.[42] reported nonsignificant differences between DOAC and LMWH in terms of fatal bleeding and fatal PE, respectively. Since data on these adverse outcomes are scant, investigations should be repeated in future studies to see if DOAC increases the rates of fatal bleeding and fatal PE events without increasing the overall PE and mortality rates. The target patient population of our included studies were generally mixed types of cancer, except some studies such as Kim et al.[11] with a focus on upper-GI cancers that found major bleeding and CRNMB rates to be higher in patients on DOAC compared to Dalteparin. Nevertheless, Agnelli et al.[6] found no difference in major gastrointestinal bleeding between groups on DOAC and LMWH. Altogether; since upper GI cancers have been shown to have higher risks of bleeding with DOACs in studies performed on upper GI patients,[11,43] these drugs should be prescribed in this population only with extreme caution until more large-scale data on this matter are available. Lastly, the follow-up durations of our included studies were heterogeneous. Ranging from 3 to 12 months with a majority of studies following the patients for 6 months; similar to the previous meta-analysis of Elbadawai et al.[30] offering a mean follow-up duration of 6.1 months; but this time window might underestimate the rates of VTE recurrence and safety outcomes so more studies with longer follow-up durations are needed in this field.

The different mechanisms of each therapy above might contribute to the observed differences in efficacy and safety. LMWH is a type of indirect anticoagulant that inhibits factor Xa through antithrombin. LMWH therapy requires an intact antithrombin pathway to employ its effect[44] which also does not require renal function to be metabolized.[45] DOACs, conversely, are direct inhibitors of specific coagulation factors, such as thrombin (factor IIa) or factor Xa, which leads to a more predictable and rapid anticoagulant effect.[46] Moreover, their absorption and half-life differences could also affect their clinical profiles.[47] The better outcomes in VTE utilizing DOACs could be linked to the more predictable and sustained anticoagulation effect, as mentioned above, potentially leading to a lower incidence of clot propagation and thromboembolic events.[47] Although LMWH has the advantage of not being metabolized by the kidney, the lack of predictable dosing could worsen the final results. In a recent meta-analysis[48] conducted on RCTs with cancer patient populations including varying degrees of kidney impairment, no differences were found in rates of recurrent VTE between patients on DOAC and LMWH; also oral anticoagulants (VKAs and DOACs) had similar results in terms of major bleeding events compared to LMWHs; however, data comparing CRNMB rates between patients on DOACs and LMWHs was not available. Nevertheless, the aforementioned details could explain the better CRNMB outcomes, as the consistent and rapid anticoagulation effect of DOAC might more likely cause minor bleeding.[47]

Our study evaluated the most recent RCTs regarding the usage of DOACs versus LMWH in patients diagnosed with CAT. The inclusion of uniform RCT studies enhances the reliability and accuracy of our findings. However, we should mention several limitations. Since the meta-analysis was based on the published articles, the publication bias could affect the final results. Moreover, high heterogeneity among the included studies, especially regarding the patient demographics and type of cancer are other restrictions in our analyses. Regarding sample size and follow-up duration, 4 of the included

studies had relatively small sample sizes, and 1 study had a shorter follow-up period of 3 months, which could introduce potential biases; to mitigate these, we conducted sensitivity analyses that confirmed the robustness of our results. Also, our data was not sufficient to execute a subgroup analysis based on cancer varieties (metastatic versus nonmetastatic and sold versus hematological). Due to the difference in VTE and bleeding probability, it is better to compare patients with different types of cancer with each other to evaluate the effects of these therapies in different populations. There should be reliable, comprehensive studies comparing different types of malignancies, across various ages, emphasizing the history of heart valve implantation, AF, and the indication of anticoagulant usage in the future.

Conclusion

In summary, our meta-analysis demonstrated the efficacy of DOACs as first-line treatment for patients diagnosed with CAT. Furthermore, the safety outcomes observed to be comparable in our analysis verified the usage of DOACs as the first-line treatment. In the future, studies with different types of DOACS are needed to guide clinicians to the best therapeutic plan for each patient with a specific type of cancer and medical history.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Asma Mousavi: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Conceptualization. **Shayan Shojaei:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Conceptualization. **Soheil Rahmati:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **Parham Dastjerdi:** Writing – review & editing, Writing – original draft, Methodology. **Mahshad Sabri:** Writing – review & editing, Writing – original draft, Methodology. **Keyvan Salehi:** Writing – review & editing, Writing – original draft, Methodology. **Kasra Izadpanahi:** Writing – review & editing, Writing – original draft, Methodology. **Homayoun Pishraft-sabet:** Writing – review & editing, Writing – original draft, Methodology. **Elmira Jafari Afshar:** Writing – review & editing, Writing – original draft, Methodology. **Mahsa Noohi Arbatan:** Writing – review & editing, Writing – original draft, Methodology. **Marc Samsky:** Writing – review & editing, Visualization, Validation, Methodology. **Kolte Dhaval:** Writing – review & editing, Visualization, Validation, Methodology. **Jamal Rana:** Writing – review & editing, Visualization, Validation, Methodology. **Toshiki Kuno:** Writing – review & editing, Visualization, Validation, Methodology. **Jay Giri:** Writing – review & editing, Visualization, Validation, Methodology. **Kaveh Hosseini:** Writing – review & editing, Visualization, Validation, Project administration, Methodology, Conceptualization.

Acknowledgment

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2025.06.022.

References

1 Weitz JI, Haas S, Ageno W, Goldhaber SZ, Turpie AGG, Goto S, Angchaisuksiri P, Nielsen JD, Kayani G, Farjat AE, Schellong S, Bounameaux H, Mantovani LG, Prandoni P, Kakkar AK. GARFIELD-VTE. Cancer associated thrombosis in everyday practice: perspectives from GARFIELD-VTE. J Thromb Thrombolysis 2020;50(2):267–77.
2 Khorana AA, Mackman N, Falanga A, Pabinger I, Noble S, Ageno W, Moik F, Lee AYY. Cancer-associated venous thromboembolism. Nat Rev Dis Primers 2022;8(1):11.
3 Falanga A, Russo L, Milesi V, Vignoli A. Mechanisms and risk factors of thrombosis in cancer. Crit Rev Oncol Hematol 2017;118:79–83.
4 Cohen AT, Katholing A, Rietbrock S, Bamber L, Martinez C. Epidemiology of first and recurrent venous thromboembolism in patients with active cancer. A population-based cohort study. Thromb Haemost 2017;117(1):57–65.
5 Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, Huisman M, King CS, Morris TA, Sood N, Stevens SM, Vintch JRE, Wells P, Woller SC, Moores L. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest 2016;149(2):315–52.
6 Agnelli G, Becattini C, Meyer G, Muñoz A, Huisman MV, Connors JM, Cohen A, Bauersachs R, Brenner B, Torbicki A, Sueiro MR, Lambert C, Gussoni G, Campanini M, Fontanella A, Vescovo G, Verso M. Caravaggio Investigators. Apixaban for the treatment of venous thromboembolism associated with cancer. N Engl J Med 2020;382(17):1599–607.
7 McBane 2nd RD, Wysokinski WE, Le-Rademacher JG, Zemla T, Ashrani A, Tafur A, Perepu U, Anderson D, Gundabolu K, Kuzma C, Perez Botero J, Leon Ferre RA, Henkin S, Lenz CJ, Houghton DE, Vishnu P, Loprinzi CL. Apixaban and dalteparin in active malignancy-associated venous thromboembolism: the ADAM VTE trial. J Thromb Haemost 2020;18(2):411–21.
8 Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, Hale D, Dunn JA, Lyman GH, Hutchinson C, MacCallum P, Kakkar A, Hobbs FDR, Petrou S, Dale J, Poole CJ, Maraveyas A, Levine M. Comparison of an oral factor xa inhibitor with low molecular weight Heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). J Clin Oncol 2018;36(20):2017–23.
9 Raskob GE, van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia D, Grosso MA, Kakkar AK, Kovacs MJ, Mercuri MF, Meyer G, Segers A, Shi M, Wang T-F, Yeo E, Zhang G, Zwicker JI, Weitz JI, Büller HR. Hokusai VTE Cancer Investigators. Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med 2018;378(7):615–24.
10 Rose DK, Bar B. Direct oral anticoagulant agents: pharmacologic profile, indications, coagulation monitoring, and reversal agents. J Stroke Cerebrovasc Dis 2018;27(8):2049–58.
11 Kim JH, Yoo C, Seo S, Jeong JH, Ryoo BY, Kim KP, Lee JB, Lee KW, Kim JW, Kim IH, Kang M, Ryu H, Cheon J, Park SR. A Phase II study to compare the safety and efficacy of direct oral anticoagulants versus subcutaneous Dalteparin for cancer-associated venous thromboembolism in patients with advanced upper gastrointestinal, hepatobiliary and pancreatic cancer: *PRIORITY*. Cancers (Basel) 2022 Jan 22;14(3):559. https://doi.org/10.3390/cancers14030559.
12 Aursulesei V, Costache II. Anticoagulation in chronic kidney disease: from guidelines to clinical practice. Clin Cardiol 2019;42(8):774–82.
13 Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
14 Schiavo JH. PROSPERO: an international register of systematic review protocols. Med Ref Serv Quarter 2019;38(2):171–80.
15 Ouzzani M, HH Fedorowicz Z, Elmagarmid A. Rayyan: A web and mobile app for systematic reviews. Syst Rev 2016;5(1):210.
16 Kaatz S, Ahmad D, Spyropoulos AC, Schulman S. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost 2015;13(11):2119–26.
17 Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thrombos Haemostas 2005;3(4):692–704.
18 Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savović J, Schulz KF, Weeks L, Sterne JAC. Cochrane Bias Methods Group. Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
19 Balduzzi S, Rucker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evid Based Ment Health 2019;22(4):153–60.
20 Cumpston MS, McKenzie JE, Welch VA, Brennan SE. Strengthening systematic reviews in public health: guidance in the Cochrane Handbook for Systematic Reviews of Interventions, 2nd edition. J Public Health (Oxf) 2022;44(4):e588–92.
21 IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. BMC Med Res Methodol 2014;14:25.

22 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327(7414):557–60.
23 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315(7109):629–34.
24 Agnelli G, Buller H, Cohen A, Gallus A, Lee T, Pak R, Raskob GE, Weitz JI, Yamabe T. Oral apixaban for the treatment of venous thromboembolism in cancer patients: results from the AMPLIFY trial. J Thrombos Haemostas 2015;13(12):2187–91.
25 Prins MH, Lensing AW, Brighton TA, Lyons RM, Rehm J, Trajanovic M, Davidson BL, Beyer-Westendorf J, Pap ÁF, Berkowitz SD, Cohen AT, Kovacs MJ, Wells PS, Prandoni P. Oral rivaroxaban versus enoxaparin with vitamin K antagonist for the treatment of symptomatic venous thromboembolism in patients with cancer (EINSTEIN-DVT and EINSTEIN-PE): a pooled subgroup analysis of two randomised controlled trials. Lancet Haematol 2014;1(1):e37–46.
26 Schrag D, Uno H, Rosovsky R, Rutherford C, Sanfilippo K, Villano JL, Drescher M, Jayaram N, Holmes C, Feldman L, Zattra O, Farrar-Muir H, Cronin C, Basch E, Weiss A. Connors JM. CANVAS Investigators. Direct oral anticoagulants vs low-molecular-weight heparin and recurrent VTE in patients with cancer: a randomized clinical trial. JAMA 2023;329(22):1924–33.
27 Planquette B, Bertoletti L, Charles-Nelson A, Laporte S, Grange C, Mahé I, Pernod G, Elias A, Couturaud F, Falvo N, Sevestre MA, Ray V, Burnod A, Brebion N, Roy P-M, Timar-David M, Aquilanti S, Constans J, Bura-Rivière A, Brisot D, Chatellier G, Sanchez O, Meyer G, Girard P, Mismetti P. CASTA DIVA trial investigators. Rivaroxaban vs dalteparin in cancer-associated thromboembolism: a randomized trial. Chest 2022;161(3):781–90.
28 Mokadem ME, Hassan A, Algaby AZ. Efficacy and safety of apixaban in patients with active malignancy and acute deep venous thrombosis. Vascular 2021;29(5):745–50.
29 Baloch MF, Adepoju AV, Falki V, Hajjaj M, Habet T, Habet K, Mahrosh A, Kundu S, Kataria J, Mathew M, Saka T, Al-Tawil M. Comparative efficacy of oral apixaban and subcutaneous low molecular weight heparins in the treatment of cancer-associated thromboembolism: a meta-analysis. Cureus 2023 Aug 14;15(8):e43447. https://doi.org/10.7759/cureus.43447.
30 Elbadawi A, Shnoda M, Mahmoud K, Elgendy IY. Efficacy and safety of direct oral anticoagulants vs. low molecular weight heparin for cancer-related venous thromboembolism: a meta-analysis of randomized trials. Eur Heart J: Cardiovasc Pharmacother 2021;7(5):380–8.
31 Haykal T, Zayed Y, Deliwala S, Kerbage J, Ponnapalli A, Malladi S, Goranta S, Samji V, Adam S. Direct oral anticoagulant versus low-molecular-weight heparin for treatment of venous thromboembolism in cancer patients: an updated meta-analysis of randomized controlled trials. Thrombos Res 2020;194:57–65.
32 Frere C, Farge D, Schrag D, Prata PH, Connors JM. Direct oral anticoagulant versus low molecular weight heparin for the treatment of cancer-associated venous thromboembolism: 2022 updated systematic review and meta-analysis of randomized controlled trials. J Hematol Oncol 2022;15(1):69.
33 Moik F, Posch F, Zielinski C, Pabinger I, Ay C. Direct oral anticoagulants compared to low-molecular-weight heparin for the treatment of cancer-associated thrombosis: updated systematic review and meta-analysis of randomized controlled trials. Res Pract Thrombos Haemostas 2020;4(4):550–61.
34 Patel T, Nadeem T, Shahbaz U, Tanveer F, Ahsan M, Saeed U, Ahmed A, Kumar V, Ibne Ali Jaffari SM, Zaman MU, Kumar S, Khatri M, Varrassi G, Vanga P. Comparative efficacy of direct oral anticoagulants and low-molecular-weight heparin in cancer-associated thromboembolism: a systematic review and meta-analysis. Cureus 2023 Jun 28;15(6):e41071. https://doi.org/10.7759/cureus.41071.
35 Song X, Liu Z, Zeng R, Shao J, Liu B, Zheng Y, Liu C, Ye W. Treatment of venous thromboembolism in cancer patients: a systematic review and meta-analysis on the efficacy and safety of different direct oral anticoagulants (DOACs). Ann Translat Med 2021;9(2):162. https://doi.org/10.21037/atm-20-8156.
36 Ueyama H, Miyashita H, Takagi H, Cruz C, Burger A, Briasoulis A, Kuno T. Network meta-analysis of anticoagulation strategies for venous thromboembolism in patients with cancer. J Thromb Thrombolys 2021;51(1):102–11.
37 Fujisaki T, Sueta D, Yamamoto E, Buckley C, Sacchi de Camargo Correia G, Aronson J, Tallón de Lara P, Fujisue K, Usuku H, Matsushita K, Mehran R, Dangas GD, Tsujita K. Comparing anticoagulation strategies for venous thromboembolism associated with active cancer: a systematic review and meta-analysis. JACC CardioOncol 2024;6(1):99–113.
38 Chen A, Stecker E, Warden BA. Direct oral anticoagulant use: a practical guide to common clinical challenges. J Am Heart Assoc 2020;9(13):e017559.
39 Chiarito M, Cao D, Cannata F, Godino C, Lodigiani C, Ferrante G, Lopes RD, Alexander JH, Reimers B, Condorelli G, Stefanini GG. Direct oral anticoagulants in addition to antiplatelet therapy for secondary prevention after acute coronary syndromes: a systematic review and meta-analysis. JAMA Cardiol 2018;3(3):234–41.
40 Guardia Martínez P, Avilés Toscano AL, Martínez Mayoral MA, Moltó Miralles J. DOAC versus VKA in patients with atrial fibrillation and bioprosthetic valves: a systematic review and meta-analysis. *Revista Española de Cardiología* (English Edition) 2023;76(9):690–9.
41 Amin A, Naeem MO, Amin L, Khaliq SU, Ahmad A, Vohra RR, Jawad S. Apixaban versus low molecular weight heparin in patients with cancer-associated venous thromboembolism: a systematic review and meta-analysis. Ann Med Surg 2012;86(8):4675–83.
42 Giustozzi M, Agnelli G, Del Toro-Cervera J, Klok FA, Rosovsky R, Martin AC, Herold J, Tzoran I, Szmit S, Bertoletti L, Becattini C, Huisman MV. Direct oral anticoagulants for the treatment of acute venous thromboembolism associated with cancer: a systematic review and meta-analysis. Thromb Haemost 2020;120(7):1128–36.
43 Kim JH, Seo S, Kim KP, Chang HM, Ryoo BY, Yoo C, Jeong JH, Lee J-L, Im H-S, Jeong H, Bang Y, Park SR. Rivaroxaban versus low-molecular-weight Heparin for venous thromboembolism in advanced upper gastrointestinal tract and hepatopancreatobiliary cancer. In Vivo (Athens, Greece) 2020;34(2):829–37.
44 Nutescu EA, Burnett A, Fanikos J, Spinler S, Wittkowsky A. Pharmacology of anticoagulants used in the treatment of venous thromboembolism. J Thromb Thrombolys 2016;41(1):15–31.
45 Bauersachs RM. LMWH in cancer patients with renal impairment—better than warfarin? Thrombos Res 2016;140. https://doi.org/10.1016/S0049-3848(16)30116-5. S160-S4.
46 Dunois C. Laboratory monitoring of direct oral anticoagulants (DOACs). Biomedicines 2021;9(5):445. https://doi.org/10.3390/biomedicines9050445.
47 Ieko M, Naitoh S, Yoshida M, Takahashi N. Profiles of direct oral anticoagulants and clinical usage-dosage and dose regimen differences. J Intensive Care 2016;4:19.
48 Alhousani M, Malik SU, Abu-Hashyeh A, Poznanski NJ, Al-Hasan S, Roth DF, Alsharedi M, Mustafa B. Using oral anticoagulants among chronic kidney disease patients to prevent recurrent venous thromboembolism: a systematic review and meta-analysis. Thrombos Res 2021;198:103–14.